REMARKS/ARGUMENTS

Remarks

I. Rejection of claims 1-28 under 35 U.S.C. § 103(a)

Claims 1-28 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Beams et al., WO 93/13055. For the following reasons, this rejection is traversed.

A. Viewed as a Whole, WO 93/13055 does not Teach or Suggest the Instant Invention

Beams et al., WO 93/13055, does not teach or suggest the compounds as claimed in the instant application. Beams et al. gives no direction to make the 3,4 double bond in a heptene carbon chain, as is claimed in the instant application, but rather proposes a large number of possible substitutions in a variable core central to the molecules. While it is acknowledged that Beams exemplifies an olefin group in examples 3 and 8, both of these examples are hex-4-enoic acids. Thus, there is no teaching in Beams et al. that would direct one of ordinary skill in the art to make the compounds of the instant invention.

B. The State of the Art, at the Time of Filing of the Instant Application Teaches Away from the Claimed Compounds.

The instant specification provides the following background at page 4, lines 7-11:

> Various attempts have been made to improve the potency and selectivity of NOS inhibitors by adding one or more rigidifying elements to the inhibitor's structure. Publications by Y. Lee et al (Bioorg. Med. Chem. 7, 1097 (1999)) and R. J. Young et al (Bioorg. Med. Chem. Lett. 10, 597 (2000)) teach that imposing conformational rigidity with one or more carbon-carbon double bonds is not a favorable approach to impart selectivity for NOS inhibitors.

Specifically, at page 1768, the Shearer reference states:

Placement of the phenyl spacer in analogues 1-6 reduces the flexibility of the backbone chain limiting the range of available binding conformations. The ortho relationship of the amino acid group and the modified guanidine functionality on the aromatic ring prevents the constrained analogues 1-3 from achieving a fully extended conformation. These structural constraints provided analogues which retained potent inhibitory properties. In contrast, the phenyl spacer in the weaker inhibitors 4-6 limits the ability of these analogues to bind in a conformation that mimics analogues 1-3. These results, while clearly not definitive, suggest that arginine based inhibitors preferentially bind in an orientation where the arginine alkyl chain is in a folded conformation that allows the appropriate spatial alignment of the amino acid and terminal guanidine moieties within the NOS active site for potent binding affinity. The design and evaluation of additional constrained analogues to further define enzyme-inhibitor interactions essential for potency and selectivity are required.

At page 600, first paragraph, the Young reference states: "It has also been suggested that imposing conformational rigidity is not a favourable approach to impart selectivity." Thus, at the time of filing of the instant application, at least two literature references were available that were skeptical of the use of rigidifying elements, such as the carbon-carbon double bonds taught in the instant application.

Significantly, two of the authors of the second literature reference (Bioorg. Med. Chem. Lett. 10, 597 (2000)), Harold F. Hodson and Richard M. Beams, are among the three inventors of WO 93-13055. Therefore, this later reference teaches away from the olefinic compounds of the present invention.

Conclusion

In view of the above, it is submitted that Claims 1-28 are in condition for allowance. Reconsideration of the rejections and objections is requested, and allowance of Claims 1-28 at an early date is solicited.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, he is cordially invited to contact Applicant's representative at the below listed number.

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